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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,561	10/27/2003	Deirdre Mary Bernadette Hickey	P32510C1D1	2410

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 10/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,561	HICKEY ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10272003*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10142005*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 18-20 and 22-24 are pending in this application.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested:

-- 5,6-TRIMETHYLENEPYRIMIDIN-4-ONE COMPOUNDS --.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of atherosclerosis, does not reasonably provide enablement for a method for the primary and secondary prevention of acute coronary events generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the

art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The scope of the claims is not adequately enabled solely based on the activity related to Lp-PLA_2 inhibition provided in the specification. First, the instant claims cover disorders that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test procedure and assay are provided in the specification in pages 49-50 and it was concluded that 'the compounds of the invention had IC_{50} values in the range of <0.1nM to 10μM', however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the prevention of all types of primary and secondary acute coronary events embraced by the instant claims. The disorders encompassed by the instant claims include e.g., cardiovascular disorders, thromboses, endothelial dysfunction, diastolic dysfunction, atherosclerosis, angina pectoris, restenoses, stroke, etc., some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Regarding secondary prevention programmes in coronary heart disease, McAlister et al. (BMJ 2001) provides that "Several questions remain to be answered. In particular, the optimal

mix of interventions, their frequency and duration, and their cost effectiveness are still unclear" (see page 961). Another reference, Iribarren et al. (Arterioscler Thromb Vasc Biol. 2005) regarding Lp-PLA_2 activity, indicates that "Additional studies are warranted to elucidate the contributions of Lp-PLA_2 bioproducts on the risk of atherothrombosis and the value of selective inhibitors of Lp-PLA_2 activity in combating atherosclerosis" (see page 220).

"Acute Coronary Events" include several types of Cardiovascular disorders, thromboses which embrace a vast array of problems, many of which are contradictory to others. Thus, the above terms could include hypertension and hypotension and further, various types of arrhythmias; angina pectoris, the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischaemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol', arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound -- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

Endothelial dysfunction is a physiological dysfunction of normal biochemical processes carried out by endothelial cell, the cells that line the inner surface of all blood vessels, arteries and veins. Compromise of normal function of endothelial cells is characteristic of endothelial dysfunction. Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function, control of volume and electrolyte content of the intravascular and extravascular spaces. Endothelial dysfunction can result from disease processes, as occurs in

septic shock, as well as from environmental factors, such as from smoking tobacco products. A state of the art reference, Lerman (2002) provides that – "Although various interventions were shown to be associated with improvement of endothelial function, little is currently known about the clinical and prognostic impact of therapeutic improvement of endothelial function" (see http://www.nhlbi.nih.gov/meetings/workshops/wise/session02_lerman.pdf). Another reference, Koren (2002) indicates that "There are no specific published guidelines for the treatment of left ventricular diastolic dysfunction" (see http://www.dcmsonline.org/jax-medicine/2002journals/Feb2002/diastolic.htm).

The scope of the method claims is not adequately enabled solely based on the activity related to Lp-PLA_2 inhibition provided in the specification. The claim language includes diseases that are known and those that are yet to be discovered, for which there is no enablement. The instant claims are drawn to 'A method for the primary and secondary **prevention** of acute coronary events ....', which includes several diseases, and therefore, the instant claim language embraces disorders not only for the treatment, but also for "prevention" which is not remotely enabled. Based on the IC_{50} range for the Lp-PLA2 inhibitory activity of the compounds (see specification pages 49-50), the instant compounds are disclosed to be useful in the primary and secondary "prevention" of acute coronary events, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. It is inconceivable from the *in vitro* data provided in the specification, as to how the claimed compounds can not

only treat but also "prevent" a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'prevention'. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study"). The instant list or disorders includes conditions such as diabetes, for which it is conventionally known that there is no cure or prevention (see e.g., http://www.hutcheson.org/Services/diabetes/index_diabetes.htm). The evidence presented in this case does not show such utilities related to 'prevention', but only warrants further study.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims are seen to encompass methods for treating as well as preventing diseases associated with acute coronary events, which include atherosclerosis, diabetes, stroke, etc. (as per specification page 2, lines 6-8).

The nature of the invention

Currently, there are no known agents with the chemotherapeutic efficacy to **prevent** all types of acute coronary events. The art does not disclose an active agent or combination of active agents, which are recognized to **prevent** the conditions cited supra. The prior art does not teach or disclose a treatment modality wherein healthy subjects are administered an active agent or agent(s) and there is evidence that none of the associated symptoms or disease state characteristics are ever manifested. The disclosure does not direct the skilled artisan to art, which satisfies the requirement for **preventing** all types of acute coronary events based on the Lp-PLA_2 inhibition activity.

The state of the prior art

There was no conclusive evidence for the **prevention** of any of the claimed diseases in the state of the art.

The level of one of ordinary skill

The level of skill is that of a MD or PhD.

The level of predictability in the art

Since the art does not disclose any chemotherapeutic preventive agents, the skilled artisan would not predict, in the absence of proof to the contrary, that the active agent(s) instantly claimed compounds are efficacious in preventing acute coronary events. The assertion of a broad application as set forth in the instant method claims necessarily requires evidence to support applicant's asserted methods. The examiner notes there are no known pharmaceutical agents recognized as **preventive** agents for the conditions claimed, and one of skill in this art could not predict, from the evidence of record, that the active agents asserted to be useful in the instantly claimed method, can indeed prevent all types of diseases associated with acute coronary events.

The amount of direction provided by the inventor

The examiner notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or references to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant preventive method. **Prevention** is seen to encompass administering the active agent to a baby or small child or healthy adult, and noting the fact that symptoms of acute coronary events such as those associated with atherosclerosis, diabetes, stroke, etc. never manifest themselves.

The existence of working examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir.

1993). There is not seen in the disclosure, sufficient evidence to support applicant's claims of prevention. There is not seen sufficient working examples or data from references of the prior art providing a nexus between that which applicant asserts as proof of a method for preventing all types of diseases associated with acute coronary events or extrapolation from the data and evidence currently provided on the record to support methods drawn to preventing such conditions.

The quantity of experimentation needed to make or use the invention

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the prevention of the claimed disorders nor indicate competent technical references in the appropriate method of preventing.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have

to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-20 and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 18, in the definition of R^3, and further the term "Het" is defined as "heterocyclyl ring **comprising** N'. In this recitation, the term "comprising" is open ended. 'Comprising' in a compound claim, leaves the claim open for the inclusion of unspecified heteroatoms. The use of the above phrase causes the claim to be broader than the invention. See *In re Fenton*, 451 F.2d 640, 171 USPQ 693 (CCPA 1971). Replacing the recitation with -- heterocyclyl ring ~~comprising~~ having N – is suggested.
2. In claim 18, the term R^2CH_2X is collectively defined as 4-fluorobenzylthio and further, a definition is provided for X (i.e., X is S). Since X definition is already included in the above expression, the recitation "X is S" in the last line is repetitive and redundant. Also, it is suggested that the definition of R^4 and R^5 would be in better form if amended as -- R^4 and R^5 together form a 4-(4-trifluoromethyphenyl)phenyl moiety --.
3. Claim 19 recites species having the following groups in place of R^2CH_2X: "(2,3-difluorobenzyl)thio" (species 1); "(3,4-difluorobenzyl)thio" (species 2) and "(2,3,4-trifuorobenzyl)thio" (species 3). There is insufficient antecedent basis for this limitation

in claim 18 on which claim 19 is dependent. According claim 18, the term 'R^2CH_2X is collectively defined as 4-fluorobenzylthio'.

4. Claim 19 recites the limitation "1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-....." (species 5, see page 6, last two lines). There is insufficient antecedent basis for this limitation in claim 18 on which claim 19 is dependent. According to claim 18, "R^3 is $C_{(1-3)}$alkyl substituted by NR^8R^9 or Het-$C_{(0-2)}$alkyl", whereas the instant species has a value of 'methyl' for R^3.
5. Claim 19 recites species having the following groups in place of the structural fragment – R^4-R^5: "(3-(4-trifluoromethyl**phenoxy**)benzyl)" (species 7, page 7, lines 3-4); "(4-(4-trifluoromethyl**phenoxy**)benzyl)" (species 8, page 7, lines 5-6) and "(4-(4-trifluoromethylbiphenyl-4-yl)**propyl**)" (species 7, page 7, lines 3-4). There is insufficient antecedent basis for this limitation in claim 18 on which claim 19 is dependent. According claim 18, the term 'R^4 and R^5 together form a 4-(4-trifluoromethylphenyl)phenyl) moiety' and further, -R^4-R^5 is attached to the N atom via a –CH_2- group.
6. Claim 19 recites the limitation "A compound as claimed in claim 18 which is: ..... or a pharmaceutically acceptable salt thereof". There is insufficient antecedent basis for the limitation "a pharmaceutically acceptable salt" in claim 18 on which claim 19 is dependent.
7. Claim 20 recites species having the following groups in place of the structural fragment – R^4-R^5: "(2-(4-trifluoromethylphenyl)**pyrid-5-yl**" (species 2); and "(2-(4-trifluoromethylphenyl)**pyramid-5-yl**" (species 3). There is insufficient antecedent basis

for this limitation in claim 18 on which claim 20 is dependent. According claim 18, the term 'R^4 and R^5 together form a 4-(4-trifluoromethylphenyl)phenyl) moiety'.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18-20 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,649,619. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims substantially overlap the reference claims. The reference claims are drawn to a species which is encompassed by the genus of structural formula (IB) of the instant claims. Further, the species claimed in the reference is present in the instant claims 19 (see 4th species) and claim 20 (see the 1st species). The reference compound is taught to be useful as pharmaceutical agents, see claims 2-3. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have had the

reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

Receipt is acknowledged of the Information Disclosure Statement filed on October 27, 2003 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

October 14, 2005

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